DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

SEP 12 2005

Rec'd 9/14/05
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RE: Health Claim Petition – Calcium and (1) Cyclic Severe Depression Associated with the Menstrual Cycle; (2) Premenstrual Dysphoric Disorder; (3) the Onset of Symptoms of Premenstrual Dysphoric Disorder; (4) Abnormal Menstrual Cycles; and (5) Polycystic Ovary Syndrome (Docket No. 2004Q-0099).

Dear Mr. Emord:

This letter responds to the health claim petition dated October 9, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Marine Bio USA, Inc. pursuant to Section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(5)(D)). The petition requested that the agency authorize health claims characterizing the relationship between the consumption of calcium and a reduced risk of: cyclic severe depression associated with the menstrual cycle; premenstrual dysphoric disorder (PMDD); the onset of symptoms of PMDD; abnormal menstrual cycles; and polycystic ovary syndrome (PCOS).

The petition proposed the following model health claims for calcium dietary supplements:

1. Calcium may reduce the risk of cyclic severe depression associated with the menstrual cycle.
2. Calcium may reduce the risk of premenstrual dysphoric disorder.
3. Calcium may reduce the risk of the onset of symptoms of premenstrual dysphoric disorder.
4. Calcium may reduce the risk of abnormal menstrual cycles.
5. Calcium may reduce the risk of polycystic ovary syndrome.

FDA informed you on October 24, 2003, that FDA was not able to acknowledge receipt of the petition and begin its preliminary review of the petition because the petition was not complete. In response, you supplied the needed information in a supplemental

2004Q-0099

PDN 1

submission received by FDA on November 25, 2003. FDA acknowledged the petition in a letter dated December 9, 2003, which initiated FDA's preliminary review of the petition. In that letter, FDA also informed you that the date by which FDA would either file or deny the petition was March 4, 2004.

In the interim, FDA evaluated the scientific evidence provided with the petition and other evidence related to your requested health claims. Based on this review, FDA determined that the scientific evidence supporting the proposed health claims does not meet the "significant scientific agreement" standard under section 403(r)(3)(B)(i) of the Act (21 U.S.C. § 343(r)(3)(B)(i)). FDA notified you of this decision and you submitted a letter dated March 2, 2004, stating that your client, Marine Bio USA, Inc., has chosen to seek FDA review of the petition as a qualified health claim. Accordingly, FDA filed the petition on March 16, 2004, as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedures on qualified health claims.[1] The agency did not receive any comments on this petition. In a letter dated June 16, 2004, you notified FDA that Marine Bio Co. Ltd. is now the petitioner of record for this petition, originally submitted by its wholly-owned subsidiary, Marine Bio USA, Inc. The initial deadline for FDA's response on the petition was October 27, 2004. After mutual agreement, the deadline for the agency's response was ultimately extended to September 12, 2005.

This letter sets forth the basis of FDA's determination that there is no credible scientific evidence to support the proposed health claims and the reasons the Agency is denying these qualified health claims. Throughout the text of this letter, the amount of calcium is expressed in weight of elemental calcium rather than weight of calcium compounds (e.g., calcium carbonate, calcium citrate).

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[2] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[3] FDA considers the data and information

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[1] "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [http://www.cfsan.fda.gov/~dms/nuttf-e.html]

[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir. 2004), *reh'g, en banc, denied*, March 9, 2004; *cert. denied*, 125 S.Ct. 310 (2004) (upholding FDA's interpretation of what constitutes a health claim).

[3] See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [http://www.cfsan.fda.gov/~dms/hclmgui4.html]

provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[4]

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[5]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[6] review articles,[7] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but can not by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, National Academy of Science, 2005). Animal and *in vitro* studies can be

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[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

[5] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects are observed or their medical records are reviewed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999). [http://www.cfsan.fda.gov/~dms/ssaguide.html]

[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[7] Review articles summarize the findings of individual studies.

[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker et al., 1991; Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[9] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S.

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[9] See *supra*, note 3.

population or target subgroup, whether study results supporting the proposed claim have been replicated,[10] and the overall consistency[11] of the total body of evidence.[12] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified calcium as the substance for the proposed health claims. Calcium, one of the essential nutrients for humans, is a component of milk and milk products (approximately 300 mg per serving) as well as other food sources (e.g., Chinese cabbage, kale, and broccoli) (IOM, 1997). Therefore, the agency concludes that the substance, calcium, is a component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition identified PMDD and PCOS as diseases and cyclic severe depression associated with the menstrual cycle and abnormal menstrual cycles as related health conditions for the proposed health claims.

PMDD is a condition marked by severe depression, irritability, and tension prior to menstruation. According to the American Psychiatric Association Diagnostic and Statistical Manual (DSM-IV), a diagnosis of PMDD requires that patients experience at least five of the symptoms that characterize PMDD. PMDD has both affective (mood) and physical symptoms, and is characterized by depressed mood, anxiety, tension, affective lability (a tendency to alternate between cheerful and somber moods), and persistent anger or irritability. Other features include decreased interest in activities,

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[10] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990; see also Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. JAMA, 294: 218-228, 2005).

[11] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300; see also Systems to rate the scientific evidence, Agency for Healthcare Research and Quality http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents (defining "consistency" as "the extent to which similar findings are reported using similar and different study designs")).

[12] See *supra*, note 3.

difficulty concentrating, lack of energy, change in appetite, headache, joint and muscle pain. The mood symptoms often cause disturbances in social relationships. Physical symptoms include weight gain, bloating, and breast tenderness. To support a diagnosis of PMDD, the symptoms must occur regularly in the luteal phase of a woman's cycle, and disappear after onset of menstruation. (The luteal phase corresponds to the period between ovulation and onset of menstruation.) While the symptoms of PMDD are similar to those of pre-menstrual syndrome (PMS),[13] they are generally more severe and debilitating.[14] PMDD affects between 3 and 8 percent of women during their reproductive years. PCOS occurs when immature follicles within the ovary bunch together to form large cysts or lumps.[15] As a result, women with PCOS often do not have menstrual periods and therefore is the most common cause of infertility. Approximately 5 to 10 percent of women in the United States have PCOS.

The agency concludes that PMDD and PCOS are diseases; therefore, the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5) with regard to the proposed health claims about calcium and PCOS, PMDD, the onset of symptoms of PMDD, and cyclic severe depression associated with the menstrual cycle. FDA considers that the claims concerning cyclic severe depression associated with the menstrual cycle and the onset of symptoms of PMDD are variations of the proposed claim about PMDD. Conversely, FDA finds that the terminology "abnormal menstrual cycles" is too vague to be considered as part of PMDD or PCOS or as an independent "disease" or "health-related condition." Therefore, the proposed claim about calcium and abnormal menstrual cycles does not meet the requirement for health claims in 21 CFR 101.14(a)(5) and the agency did not consider this claim in its evaluation of the petition.

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling,

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[13] PMS is a group of symptoms related to the menstrual cycle including fatigue, trouble sleeping, headaches, irritability, anxiety and/or depression. While PMS is estimated to affect up to 75% of women during their childbearing years, an exact cause of PMS has not been determined. See http://www.nlm.nih.gov/medlineplus/ency/article/001505.htm

[14] http://www.nlm.nih.gov/medlineplus/ency/article/007193.htm

[15] http://www.nichd.nih.gov/about/womenhealth/infertility.cfm

under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))).

The petition stated that calcium is an essential mineral that has a multitude of vital biological roles and also asserted that there is an absolute lack of any reports of clinically significant adverse reactions attributed to dietary calcium. Further, the petition stated that the final rule authorizing the health claim about calcium and osteoporosis concluded that calcium complies with the requirements of 21 CFR 101.14(b)(3)(ii). The petition stated that FDA has determined that ten calcium compounds have been demonstrated to be safe and lawful for use in dietary supplement. 58 FR at 2670 citing 56 FR at 60691. The petition also stated that calcium has prior sanctioned status as safe and lawful under the Act. Further, the petition noted that the North American Menopause Society, in its 2001 Consensus Opinion, stated that the side effect profile from recommended levels of calcium intake is insignificant and that no serious side effects are associated with those levels, and that the Physicians' Desk Reference (PDR) reported that calcium supplements are generally well tolerated. The petition claimed that daily dietary supplementation of 1,200 mg/day of elemental calcium is effective in reducing the risk of cyclic severe depression associated with the menstrual cycle, PMDD, the onset of symptoms of PMDD, abnormal menstrual cycles, and PCOS.

It is not necessary for FDA to make any determination about the safety of calcium in this letter because the agency is denying the proposed claims for lack of credible evidence, as discussed in sections II and III.

II. The Agency's Consideration of a Qualified Health Claim

FDA used incident cases of PMDD and PCOS for evaluating risk reduction of these diseases, including, for PMDD, cyclic severe depression associated with the menstrual cycle and the onset of symptoms of PMDD. FDA identified no surrogate endpoints to use in assessing PMDD and PCOS risk reduction.

The petition cited 63 publications as evidence to substantiate the relationship for the proposed claims (see bibliography from docket number 2004Q-0099, 04q-0009-qhc001-002-exhibit-01.vol1.pdf). These publications consisted of three book chapters from the Institute of Medicine, National Academy of Sciences; 14 review articles/editorials; two Federal Register rules regarding calcium and osteoporosis; 27 studies on calcium bioavailability that did not study the substance-disease relationships; 6 studies on calcium and bones not related to the proposed claims; 6 studies on the relationship between calcium and other diseases (e.g., renal failure and hyperthyroidism) not related to the proposed claims; 4 intervention studies on calcium intake and mitigation of PMS

symptoms; and 1 study on calcium intake and the mitigation of symptoms associated with PCOS.

Below, we assess all of the available scientific information identified in relation to the proposed claims.

A. Assessment of Review Articles, Meta-Analyses and Abstracts

Although useful for background information, the review articles, meta-analysis, and abstracts do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analysis, and abstracts supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of the Intervention Studies

FDA identified a total of five intervention studies for its review of this qualified health claim (Alvir et al., 1991; Thys-Jacobs et al., 1989; Penland et al., 1993; Thys-Jacobs et al, 1998; Thys-Jacobs et al., 1999). Alvir et al. (1991) was a reanalysis of the exact study described by Thys-Jacobs et al. (1989), therefore only four intervention studies were evaluated for the proposed claims.

Three intervention studies evaluated the relationship between calcium supplements and symptoms of PMS (Thys-Jacobs et al., 1989; Thys-Jacobs 1998; Penland et al., 1993). Thys-Jacobs et al. (1989) and Thys-Jacobs (1998) provided women with PMS a placebo or calcium supplement for three months. Both studies reported that calcium supplementation significantly reduced symptoms associated with PMS (e.g., irritability, crying, mood swings, depression, crying, violent tendencies, water retention, and menstrual pain). Penland et al. (1993) reported that higher levels of calcium consumption reduced many PMS symptoms (e.g., mood swings, concentration, water retention, and menstrual pain) in healthy women. None of these three intervention studies measured the risk of developing PMDD or PCOS with calcium supplementation. Furthermore, no evidence was provided to the agency to demonstrate that calcium supplementation in women with PMS would decrease their risk of developing PMDD or PCOS. FDA conducted its own literature review and has determined that there is no evidence to suggest that mitigating the symptoms of PMS would reduce the risk of developing

PMDD or PCOS.[16] Therefore, the Agency cannot draw any scientific conclusions from these studies about a relationship between calcium and PMDD or PCOS.

The fourth intervention study, Thys-Jacobs et al. (1999), treated 13 women diagnosed with PCOS with supplements containing both calcium and vitamin D and evaluated their androgen hormone levels, menstruation, and ovulation. Because the women were already diagnosed with PCOS, it was not possible to determine whether the supplementation would reduce the risk of developing PCOS. Health claims characterize the relationship between a substance and a reduction in risk of contracting a particular disease.[17] Accordingly, these claims are necessarily about reducing the risk of a disease in people who do not already have such disease. As a result, FDA considers evidence from studies in women already diagnosed with PCOS only if it is scientifically appropriate to extrapolate to women who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the PCOS-diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Given that such evidence is not available, the agency cannot draw any scientific conclusions from the Thys-Jacobs et al. (1999) study. Furthermore, the study contained no control group; thus, we do not have a comparison for the intervention of vitamin D and calcium supplementation and therefore cannot draw any scientific conclusions from this study. In addition, vitamin D is involved with the absorption and metabolism of calcium and may confound results (Institute of Medicine, National Academy of Science, 1997). Therefore, because calcium was given in combination with vitamin D, this study does not provide information about the independent effect of calcium in mitigating the symptoms of PCOS.

C. Assessment of the Observational Studies

No observational studies were submitted by the petitioner about a relationship between Calcium and PMDD or PCOS risk reduction, nor did the agency identify any relevant observational studies from a literature search.

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[16] Even if a study on PMS could provide scientific information about PMDD or PCOS, these three studies did not provide any information on reduction of risk. While these studies reported the mitigation of symptoms of PMS, there is no evidence to demonstrate that calcium supplements may reduce the risk of getting the symptoms of PMS. Assuming studies on PMS could provide scientific information about PMDD or PCOS, in order to evaluate risk reduction, FDA would consider evidence from studies in women already diagnosed with symptoms of PMS only if it were scientifically appropriate to extrapolate to women who do not have the symptoms. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in women with symptoms of PMS are the same as the mechanism(s) for risk reduction effects in women who do not have the symptoms; and (2) the substance affects these mechanisms in the same way in both women with and without PMS symptoms. Given that such evidence is not available, the agency would not be able to draw any scientific conclusions about reduction of risk from the three studies, even if it were appropriate (Thys-Jacobs et al., 1989; Thys-Jacobs 1998; Penland et al., 1993).

[17] See *supra*, note 2.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[18] and the overall consistency[19] of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

As discussed in Section II, there is no scientific evidence to support the proposed claims for PMDD or PCOS. Based on the review of the total body of publicly available scientific evidence, FDA concludes that there is no credible evidence to support these claims.

IV. Agency's Consideration of Disclaimers or Qualifying Language

FDA considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception here, where there is no credible evidence to support any of the claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the false message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), *cert denied,* 423 U.S. 827 (1975);

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[18] See *supra*, note 10.
[19] See *supra*, note 11.

Continental Wax Corp. v. FTC, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States,* 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.,* 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.,* 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

V. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with the petition, and other pertinent scientific evidence and information, FDA concludes that there is no credible evidence to support the proposed health claims. Thus, FDA is denying the petition for qualified health claims based on the following proposed health claims:

1. Calcium may reduce the risk of cyclic severe depression associated with the menstrual cycle.
2. Calcium may reduce the risk of premenstrual dysphoric disorder.
3. Calcium may reduce the risk of the onset of symptoms of premenstrual dysphoric disorder.
4. Calcium may reduce the risk of abnormal menstrual cycles.
5. Calcium may reduce the risk of polycystic ovary syndrome.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement for a health claim.

Sincerely,

Barbara Schneeman

Barbara O. Schneeman, Ph.D.
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